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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/257,272	02/25/1999	JING-SHAN HU	PF112P2D2	1980

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HUMAN GENOME SCIENCES INC
9410 KEY WEST AVENUE
ROCKVILLE, MD 20850

EXAMINER
LANDSMAN, ROBERT S

ART UNIT	PAPER NUMBER
1647	32

DATE MAILED: 04/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/257,272	HU ET AL.	
	Examiner	Art Unit	
	Robert Landsman	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-48,65-96 and 113-272* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-48,65-96 and 113-272* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 30 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Formal Matters

A. The Supplemental Information Disclosure Statement, filed 2/4/03, has been entered into the record.

B. The Supplemental Information Disclosure Statement, filed 8/16/02, has been entered into the record.

C. Amendment D, filed 2/4/03, has been entered into the record. Claims 33-272 were pending. However, in Amendment D, Applicants cancelled claims 49-64 and 97-112. Therefore, claims 33-48, 65-96 and 113-272 are pending and are the subject of this Office Action.

D. The Terminal Disclaimer, filed 2/4/03, is proper and has been entered into the record.

E. All Statutes under 35 USC not found in this Office Action can be found, cited in full, in a previous Office Action.

2. Statutory Declarations

A. The Examiner stated in the Office Action dated 8/13/02, that Statutory Declarations are not proper subject matter for an IDS. Applicants argued that this is incorrect, citing 37 CFR 1.56(a) and 37 CFR 1.98(a)(1), stating that "an information disclosure statement shall include a list and a legible copy 'of all patents, publications, applications, or other information submitted for consideration by the Office.'" In view of this argument, the Examiner will consider these Declarations. However, they will not be printed along with the other references on the Forms PTO-1449.

3. Double Patenting

A. The rejection of any and all claims in the present application as claiming the same subject matter as claims 1-5, 7-11 and 14 of US Patent No. 5,932,540 has been withdraw in view of Applicants' filing of a proper Terminal Disclaimer.

B. The claims as listed on pages 3-5, paragraphs B-F of the Office Action dated 8/13/02 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting over one or more claims of US Application Nos. 09/219,442; 09/935,726; 08/465,968 and 09/107,997. Applicants state that they will file a Terminal Disclaimer if and when claims to one or more of these copending applications become allowable. 09/623,725 is ABN.

Considering 09/935,726 and 09/107,997, each with regard to the present invention, 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

C. The Examiner stated in the Office Action dated 8/13/02 that claims 33-48, 65-96 and 113-272 are provisionally rejected under the judicially created doctrine of double patenting over claims 14, 15, 18-20 of copending Application No. 10/060,523.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: both the claims of '523 and of the instant application recite proteins of SEQ ID NO:2 or 4, or fragments thereof as well as methods of administering the VEGF-2 of SEQ ID NO:2 or 4, or fragments thereof, to a patient. The claims of the present application recite a method of stimulating angiogenesis and endothelial cell proliferative activity, whereas the methods of '523 do not provide a specific limitation of the disease to be treated. However, administering the VEGF-2 of SEQ ID NO:2 or 4, or a fragment of ATCC No. 75698 or 97149, to a patient would inherently have the same effects in the populations of both applications since the administered compounds are identical. Although the conflicting claims are not identical, they are not patentably distinct from each other because the process steps of administering VEGF-2 are the same regardless of the purpose (Ex parte Novitski, 26 USPQ 1391). As claimed, the population of the present invention falls entirely into the population of the present application.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804. In addition, the Examiner inadvertently stated that 10/060,523 is a divisional of 09/879,225. This is incorrect. Application 10/060,523 is a divisional of 08/207,550, as 09/879,225 does not belong to this series of cases.

D. Claims 33-48, 65-96 and 113-272 are provisionally rejected under the judicially created doctrine of double patenting over claim 69-86 of copending Application No. 10/127,551. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: both the claims of '551 and of the instant application recite VEGF-2 proteins of SEQ ID NO:2 and 4, or fragments thereof, as well as methods of administering the VEGF-2 of SEQ ID NO:2 or 4, or fragments thereof, to a patient. The claims of the present application recite a method of stimulating angiogenesis and endothelial cell proliferating activity, whereas the methods of '551 recite methods of stimulating endothelial cell proliferation. However, administering the VEGF-2 of SEQ ID NO:2 or 4 to a patient would inherently have the same effects in the populations of both applications since the administered compounds are identical. Although the conflicting claims are not identical, they are not patentably distinct from each other because the process steps of administering VEGF-2 are the same regardless of whether the purpose is to stimulate angiogenesis or proliferation of endothelial cells (Ex parte Novitski, 26 USPQ1391). As claimed, the population of '551 falls entirely into the population of the present application. Regardless, there would be expected to be overlap in these populations.

Furthermore, there is no apparent reason why applicant would be prevented from presenting claims corresponding to those of the instant application in the other copending application. See *In re Schneller*, 397 F.2d 350, 158 USPQ 210 (CCPA 1968). See also MPEP § 804.

Furthermore, 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

E. Claims 33, 34, 49, 50, 65, 66, 81, 82, 97, 98, 113, 114, 129, 130, 145, 146, 161, 162, 177, 178, 193, 194, 209, 210, 225, 226, 241, 242, 257 and 258 are provisionally rejected under the judicially created doctrine of double patenting over one or more claims of copending Application No. 10/084,488. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: the claims of both applications recite the polypeptide of SEQ ID NO:2 or 4, which are encoded for by the nucleic acid molecules of SEQ ID NO:1 and 3, respectively. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

F. Claims 38-48, 70-80, 86-96, 118-128, 134-144, 150-160, 166-176, 182-192, 198-208, 214-224, 230-240, 246-256 and 262-272 are provisionally rejected under the judicially created doctrine of double patenting over claims 38 and 42-71 of copending Application No. 09/499,468. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

The subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending application and the instant application are claiming common subject matter, as follows: both the claims of '468 and of the instant application recite methods of administering the VEGF-2 of SEQ ID NO:2 or 4, or fragments thereof, to a patient. The claims of the present application recite a method of stimulating angiogenesis, or proliferating endothelial cells whereas the methods of '468 recite methods of stimulating photoreceptor cells. However, administering the VEGF-2 of SEQ ID NO:2 or 4, or a fragment thereof, to a patient would inherently have the same effects in the populations of both applications since the administered compounds are identical. Although the conflicting claims are not identical, they are not patentably distinct from each other because the process steps of administering VEGF-2 are the same regardless of whether the purpose is to stimulate angiogenesis, proliferation of endothelial cells, or stimulation of photoreceptor cells (Ex parte Novitski, 26 USPQ 1391). The claims of the instant invention define a patient population in terms of having a specific disease and '468 do provide a dosing range. However, a population of each application may fall into the population of each of the other applications (i.e. there would be expected to be overlap in these populations).

4. Claim Rejections - 35 USC § 112, first paragraph - enablement

A. The rejection of claims 97-192 under 35 USC 112, first paragraph, as not being enabled since Applicants did not recite that all restrictions will be removed has been withdrawn in view of this statement being made over the Attorney's signature.

B. Claims 33-48, 65-96 and 113-272 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 6-7 of the Office Action dated 8/13/02. First, the Examiner apologizes for making the rejection over the limitation "at least 30 contiguous amino acids" as this limitation is not recited in the present claims. However, regarding the other issues, Applicants have amended the claims to recite "endothelial cell proliferating activity" and argue that, based on homology to the PDGF/VEGF family, 8 cysteines and a consensus sequence (SEQ ID NO:8) would be required to maintain biological activity. However, Applicants have not demonstrated that these are the only amino acids critical to maintain biological activity, or, more accurately, endothelial cell proliferating activity. It would not be expected that all biological activities of a protein are based on the same exact residues of a protein. For example, a biological activity of producing an antibody would likely require different residues than for stimulating endothelial cell proliferation. The requirement for the conserved motifs has not been shown to be sufficient for endothelial cell proliferation. Therefore, due to this lack of guidance and working examples, it would not be predictable to the artisan how to make a protein according to the present invention which has endothelial cell proliferating activity. The list of conservative amino acid substitutions on page 20 of the specification does not provide sufficient guidance as to what other residues can be altered to maintain the desired activity, nor have Applicants shown that these substitutions, in fact, can be made while maintaining the desired function. If they were, then Applicants *may* be entitled to the full-length proteins and a certain percentage of conservative substitutions only. Though Examples 5 and 6 do provide an assay to determine endothelial cell proliferation activity, the number of possible proteins to be screened using this assay is undue in view of the minimal guidance and working examples of proteins having this activity. It cannot be determined by the Examiner if the only enabled VEGF-2 (e.g. Examples 5 and 6) is that of **SEQ ID NO:2 or SEQ ID NO:4**. Clarification of this issue is respectfully requested. Until this issue is clarified, since there is no disclosure of the use of SEQ ID NO:4 or any of its fragments, including those which are **90 or 95%** identical to these proteins, Applicants are not enabled for these.

Furthermore, in Examples 5 and 6, Applicants only demonstrate that one VEGF-2 protein is capable of stimulating endothelial cells. First, it is not clear if this protein is part of SEQ ID NO:2 or 4. Second, these examples only demonstrate that a protein lacking the first **46 residues** is capable of producing such an effect. Applicants have not demonstrated, as seen in, for example, claim 193, that proteins having greater than only the first 46 residues deleted have the desired activity. Therefore, since the fragments themselves of claim 193 and others have not been shown to have the desired effect (e.g. residues 71-396), it would not be predictable to the artisan what fragments which are only 90 or 95% identical to these fragments, would have the desired activity.

In addition, Applicants are not enabled for the "**mature**" form of VEGF-2, nor for any "**proprotein**" of VEGF-2 since they have only provided guidance and working examples of the full-length of one VEGF-2. The sequence of any mature form or proprotein have not been disclosed in the specification. Applicants have not provided any guidance or working examples of a "mature" VEGF-2 protein, or of a "proprotein" of VEGF-2. In other words, the exact sequence of the mature and proprotein forms are not disclosed in the specification. Therefore, not only are these proteins, or methods of using these proteins not enabled, but claims reciting "90 or 95%" of these forms are also not enabled since it is not taught, nor predictable, what the full-length forms are in order to make the appropriate changes.

Therefore, the breadth of the claims is excessive with regard to Applicants claiming all fragments of SEQ ID NO:2 or 4 which have endothelial cell proliferating activity. Applicants have only provided guidance and working example of one VEGF fragment (Examples 5 and 6), though it is not clear if that is of SEQ ID NO:2 or 4. No other guidance has been provided to enable the breadth of the claims with regard to % identitiy, mature forms, proprotein forms, fragments comprising residues 71-396 of SEQ ID NO:2, or those comprising SEQ ID NO:8. Therefore, it is not predictable to the artisan how to make proteins with endothelial cell proliferating activity other than that in Examples 5 and 6. For these reasons, the Examiner holds that undue experimentation is required to practice the invention as claimed.

5. Claim Rejections - 35 USC § 112, first paragraph – written description

A. Claims 33-48, 65-96 and 113-272 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on pages 7-8 of the Office Action dated 8/13/02. First, the Examiner apologizes for making the rejection over the limitation "at least 30 contiguous amino acids" as this limitation is not recited in the present claims. However, regarding the other issues, Applicants have amended the claims to recite "endothelial cell proliferating activity" and argue that, as stated above, based on homology to the PDGF/VEGF family, 8 cysteines and a consensus sequence (SEQ ID NO:8) would be required to maintain biological activity. However, Applicants have not demonstrated that these are the only amino acids critical to maintain biological activity, or, more accurately, endothelial cell proliferating activity. It would not be expected that all biological activities of a protein are based on the same exact residues of a protein. For example, a biological activity of producing an antibody would likely require different residues than for stimulating endothelial cell proliferation. The requirement for the conserved motifs has not been shown to be sufficient for endothelial cell proliferation. The list of conservative amino acid substitutions on page 20 of the specification does not provide sufficient guidance as to what other residues can be altered to maintain the desired activity, nor have Applicants shown that these substitutions, in fact,

can be made while maintaining the desired function. If they were, then Applicants *may* be entitled to the full-length proteins and a certain percentage of conservative substitutions only. Though Examples 5 and 6 do describe one example of a VEGF-2 protein on endothelial cell activity, it cannot be determined by the Examiner if the only enabled VEGF-2 (e.g. Examples 5 and 6) is that of **SEQ ID NO:2 or SEQ ID NO:4**. Clarification of this issue is respectfully requested. Therefore, if this example is using only one fragment of SEQ ID NO:2 which comprises residues 47-396, then this is the only fragment that Applicants have adequately described. Since there is no disclosure of the use of SEQ ID NO:4 or any of its fragments, including those which are **90 or 95%** identical to these proteins, these proteins and fragments are not adequately described as they relate to a claimed activity.

B. Claims 33-48, 65-96 and 113-272 remain rejected under 35 USC 112, first paragraph, for the reasons already of record on page 8 of the Office Action dated 8/13/02. Applicants argue that "mature" and "proprotein" are defined on pages 9 and 11 of the specification. Applicants argue that they are inherently in possession of these forms of the proteins and that all the information required to obtain these proteins is provided in the given in the amino acid sequence. The Declaration by Dr. Aaronson is, respectfully, not found persuasive. The mature or proprotein form of a given protein is of a specific sequence. Though these forms may be inherently formed in a given expression system, for example, the exact sequce is still not known. Therefore, the artisan would not know when they were in possession of the mature or proprotein form of VEGF.

The instant specification fails to describe that portion of a protein which is the "**mature**" portion, or what constitutes a "**proprotein**." Applicant is claiming a very specific species which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The structure of a "mature form of a polypeptide" cannot be predicted on the basis of the amino acid sequence of the entire protein since the protein may be proteolytically cleaved in vivo, as well as being differentially processed based on which in tissue the protein is expressed. The claims are directed to a species of protein, the structure of which cannot be determined or predicted from full-length amino acid sequence and the specification does not evidence isolation or conception of the structure of the "mature form of a polypeptide," or the "preprotein form." Therefore, the specification does not provide an adequate written description of a mature protein, or preprotein form and thus the claimed invention, to the extent that it reads upon mature protein or proprotein was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

6. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (703) 306-3407. The examiner can normally be reached on Monday - Friday from 8:00 AM to 5:00 PM (Eastern time) and alternate Fridays from 8:00 AM to 5:00 PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Official papers filed by fax should be directed to (703) 308-4242. Fax draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert Landsman, Ph.D.
Patent Examiner
Group 1600
April 15, 2003

ROBERT LANDSMAN
PATENT EXAMINER